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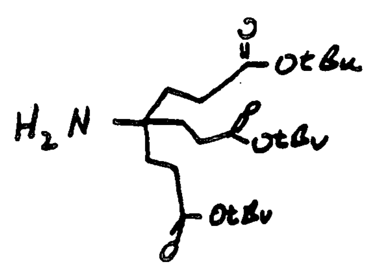

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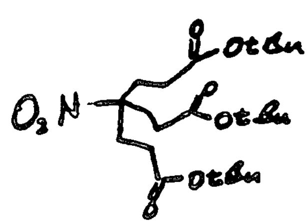

(II)

(57) Abstract

A method for forming cascade polymers specifically utilizing the amine monomer of formula (I). The monomer is made by initially reacting nitromethane and $CH_2=CHCO_2$-TBu by nucleophilic addition to form the triester nitrotrialkanoate of formula (II), and then reducing the nitrosubstituent to afford the said amine monomer.

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T-BUTYL CASCADE POLYMERS

Technical Field

The present invention relates to the field of polymer chemistry and, more specifically with regard to the field of cascade or dendritic polymer chemistry. These polymers are based upon the application of mathematical progressions to organic synthesis and thereby possess well-defined molecular topologies.

BACKGROUND OF THE INVENTION

The field of cascade polymer chemistry is expanding the traditional synthetic limits into the meso-macro-molecular frontier. Such polymers possess well-defined molecular topologies as they can be constructed in discrete layers rendering upon the molecule discrete, symmetric and consistent chemical characteristics.

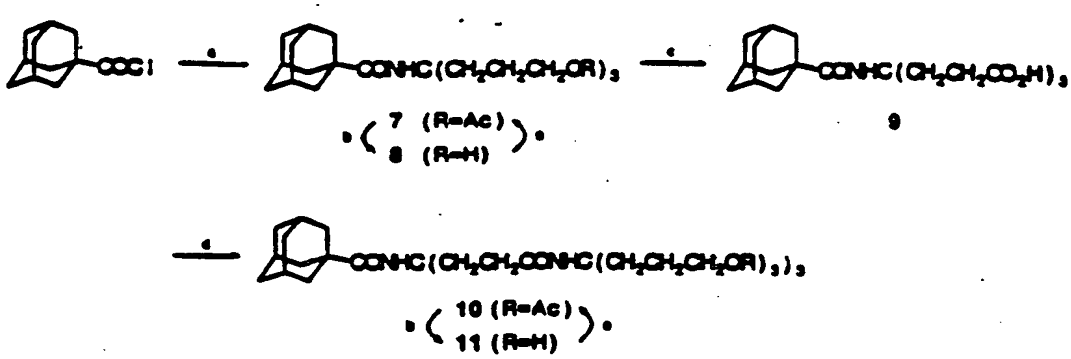
These polymeric structures provide specific micellar molecules.

The synthesis and spectral features of cascade polymers, also referred to as arborols possessing two-, three- and four-directional microenvironments with functionalized polar outer

surfaces, have been recently reported(1-8). Depending on their molecular shape, many of these macromolecules aggregate to form gels or show novel micellar characteristics in aqueous solution (3,7,8). In view of an interest in generating a spherical hydrophilic surface with a compact lipophilic core, the present invention provides a cascade system which in one embodiment emanates from a central adamantane core. This core includes bridgehead positions which have suitable geometry to mimic a tetrahedral nucleus and can be envisioned as an extended methane core. Such a core is an ideal starting point toward four-directional cascade polymers.

In constructing such spherical polymers, several further problems were uncovered. One such problem related to the generation of a tri-branched monomer which would not cyclize. More specifically, to provide tri-valent branching from a single branch of a polymer, at least two qualities are required. First, there must be directionality such that the monomer combines with the branch so as to expose three branch binding sites for further tiering of the macromolecule. The branches of the macromolecule extending from a central core must

also extend sufficiently to be able to allow further reactions therewith for the additional tiering while not cyclizing onto themselves. Cyclizing removes branches from being chemically reactive thereby causing a dead-end to the tiering process. For example, the following reaction sequence generated the polymeric product set forth below.



Attempted oxidation of compound 11 by a RuO_2 procedure of Irngartinger, et al.(9) resulted in limited success in that complete oxidation was not reproducible.

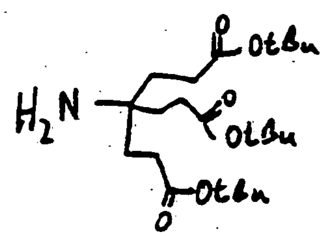
Applicant herein provides novel monomers which are ideal in that they do not cyclize and further can be used in a cascade system for producing macromolecular monomers through tetradirectional polymers, particularly

on an adamantane, methane equivalent, or four-directional core.

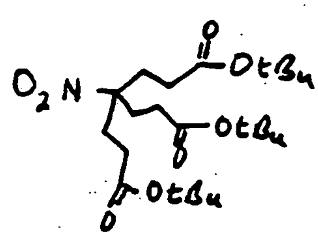
Further, the present invention provides novel four-directional spherical dendritic macromolecules based on adamantane made in accordance with the novel method set forth herein.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is a method forming an amine monomer of the formula



by the steps of reacting nitromethane and CH_2=$CHCO_2$-TBu by nucleophilic addition to form the triester nitrotrialkanoate of the formula

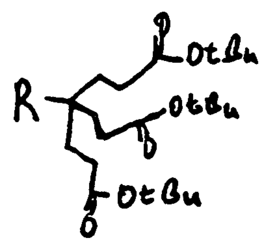


and reducing the nitrosubstituent to said amine monomer.

Further in accordance with the present invention the novel amine monomer can be used to create several novel one, two, three, or four-directional polymers based on the adamantane, or similar core.

DETAILED DESCRIPTION OF THE INVENTION

The present invention generally will provide a monomer of the formula



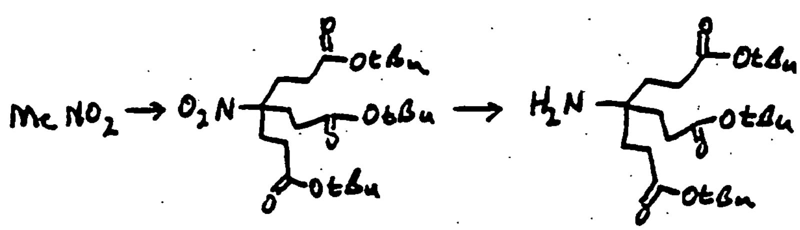
wherein R is selected from the group consisting essentially of NH_2 and NO_2. This novel compound is a building block for novel cascade polymers made in accordance with the inventive method set forth below. Products made in accordance with the present invention can be used in various fields, such as pharmaceutical chemistry, as micelles. However these compounds are used to make unimolecular micelles as opposed to multi-molecular micelles, previously known in the art.

These monomeric micelles generally have a core and branching which leads from the core. In accordance with the present invention, the branching can be tetra-directional extending from the four bridgehead positions of the core and can be tiered or layered such that a first layer of branching can be combined with the core and then subsequent layers can be added to provide a well-defined molecular topology.

More specifically, as discussed above, attempted oxidation of the arborol of the formula

 $CONHC[CH_2CH_2CONHC(CH_2CH_2CH_2OR)_3]_3$

by the RuO_2 procedure discussed above met with limited success in that complete oxidation was not reproducible. To circumvent this problem as well as to shorten the overall iterative procedure, the novel building block di-tert-butyl 4-amino-[2-(tert-butoxycarbonylethyl]-heptanedioate was prepared by the following scheme.



A key factor was the bulky nature of the <u>tert</u>-butyl ester, so it was necessary to prevent lactam formation during reduction of the nitro functionality. That is, the following reaction did not occur under the condition conducted in accordance with the present invention.

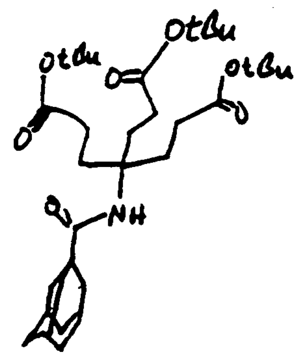
An attempt to synthesize the nitro ester precursor by modification of the procedure reported by Bruson and Riener(10) using <u>tert</u>-butyl acrylate in place of the acrylonitrile resulted in a poor yield of about 5%. To circumvent this sluggish nucleophilic addition, the reaction temperature was elevated during the initial addition phase and then maintained at about 70° to 80°C for one hour. This modification resulted in a 72% yield of the desired triester, which was confirmed by ^{13}C NMR by the peaks for the quaternary and carbonyl carbons at 92.1 and 170.9 ppm, respectively. The ^{1}H NMR spectrum showed a singlet at 1.45 ppm assigned to $(CH_3)_3CO$ in a multiplet at 2.21 ppm for the methylene protons. Analysis of the crystal structure ultimately confirmed the analysis.

The prior art discusses diverse reduction conditions for the conversion of nitroalkanols to aminoalkanols(11). The use of

platinum, palladium, or Raney nickel catalyst all resulted in very poor yields and gave mostly recovered nitrotrialkanoate compound. However, a reduction with specially generated T-1 Raney nickel by the process of Domingues, et al.(12) at elevated temperatures (ca. 60°C) gave an 88% yield of the aminoester after purification. Successful reduction was confirmed by ^{13}C NMR by an upfield shift for the quaternary carbon at 52.2 ppm. The ^{1}H NMR spectrum of the aminotrialkanoate showed a singlet at 1.44 ppm for the tert-butyl group, multiplets at 1.68 and 2.26 ppm for the methylene protons and a broad singlet at 5.49 ppm for the amino moiety.

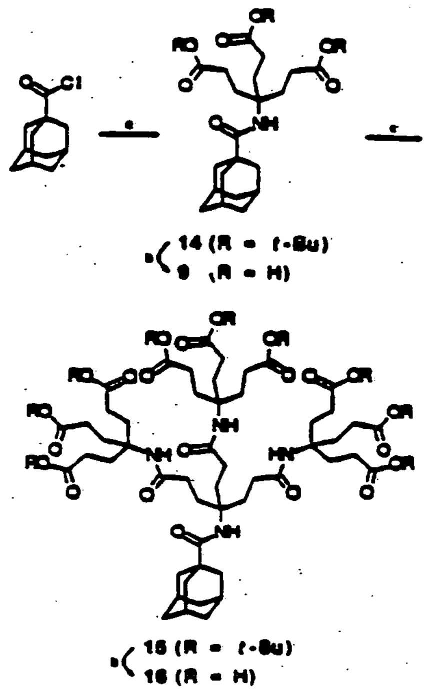
Since related alkyl esters of the aminotrialkanoate could not be prepared because of facile intramolecular lactam formation during the hydrogenation of the nitro moiety, the tert-butyl ester is ideal in that no cyclization was observed. The advantages of the tert-butyl ester are: a) reduced number of overall steps for cascade synthesis; b) easy preparation on a large scale; c) facile hydrolysis to the desired acids in nearly quantitative yield; and d) the poly tert-butyl esters were easily purifiable solids.

An example of the use of the <u>tert</u>-butyl ester in a cascade synthesis is as follows. Treatment of adamantanecarbonyl chloride with the aminotrialkanoate as set forth above furnished 71% yield of the desired triester (amine monomer) of the formula



This structure was confirmed by ^{13}C NMR by the peaks at 172.8 (ester), 177.4 (CONH), and 56.7 ppm (side-quaternary carbon). Hydrolysis of the ester to a triacid was accomplished with about 100% yield by treatment with formic acid. It was identical in all respects to a sample prepared by the above procedure. Application of peptide coupling procedures known in the art of the acid with the aminotrialkanoate in the presence of DCC and 1-hydroxybenzotriazole in dry dimethyl formamide (DMF) afforded a 61% yield of a

nonaester(13). The following scheme summarizes the reaction sequence



The presence of the structure was confirmed by ^{13}C NMR showing two carbonyl peaks at 172.6 (ester) and 177.0 ppm (CONH) as well as the peaks for the side-chain quaternary carbons at 57.6 and 57.0 ppm thereby confirming the transformation. The specific assignment of internal and external methylene signals was based on the intensity ratios as well as the fine shape, the internal methylenes being broader. The final acid was obtained in a 95% yield by the treatment of the ester with formic acid. The absence of the tert-butyl groups in the NMR

spectra and the shift for the carbonyl, 172.6 ppm (ester) to 177.6 ppm (acid) supports the conclusion that hydrolysis occurred.

Experimental Section

General Comments. Melting point data were obtained in capillary tubes with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CHCl^3$, except where noted, with Me_4Si as the internal standard (δ = 0 ppm), and recorded at either 80 or 360 MHz. Infrared spectral data were obtained on an IBM IR-38 spectrometer. Elemental analyses were performed by MicAnal Laboratories in Tucson, Arizona.

Di-tert-butyl 4-Nitro-4-[2-(tert-butoxycarbonyl)ethyl]heptanedioate. A stirred solution of $MeNO_2$ (6.1 g, 100 mmol), Triton B (benzyltrimethylammonium hydroxide, 40% in MeOH; 1.0 mL) in dimethoxyethane (DME; 20 mL) was heated to 65° to 70°C. tert-Butyl acrylate (39.7 g, 310 mmol) was added portion wise to maintain the temperature at 70° to 80°C. Additional Triton B (2x1 mL) was added when the temperature started to decrease; when the addition was completed, the mixture was maintained at 70° to 75°C for one

hour. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$ (200 mL), washed with 10% aqueous HCl (50 mL) and brine (3x50 mL), and dried ($MgSO_4$). Removal of solvent *in vacuo* gave a pale yellow solid, which was crystallized (95% EtOH) to afford a 72% yield of the triester, as white microcrystals: 33 g; mp 98-100°C; ^1H NMR δ 1.45 (s, CH_3, 27 H), 2.21 (m, CH_2, 12 H); ^{13}C NMR δ 27.9 (CH_3), 29.7 (CH_2CO), 30.2 (CCH_2), 80.9 (CCH_3), 92.1 (O_2NC), 170.9 (CO); IR (KBr) 1542 (NO_2), 1740 (CO) cm^{-1}. Anal. Calcd for $C_{22}H_{39}O^8N$: C, 59.35; H; 8.76; N, 3.14. Found: C, 59.27; H, 9.00; N, 3.14.

Di-*tert*-butyl 4-Amino-4-[2-(*tert*-butoxycarbonyl)ethyl]heptanedioate. A solution of the above synthesized nitro triester (4.46 g, 10 mmol) in absolute EtOH (100 mL) with T-1 Raney Ni_{12} (4.0 g) was hydrogenated at 50 psi and 60°C for 24 hours. The catalyst was cautiously filtered through Celite. The solvent was removed *in vacuo*, affording a viscous liquid, which was column chromatographed (SiO_2), eluting with EtOAc to give a 88% yield of the amino triester as a white crystalline solid: 3.7 g; mp 51-52°C; ^1H NMR δ 1.44 (s, CH_3, 27 H), 1.78 (m, CH_2, 12 H); ^{13}C NMR δ 27.8 (CH_3), 29.8 (CH_2CO), 34.2 (CCH_2), 52.2

(H_2NC), 80.0 (CCH_3), 172.8 (CO); IR (KBr) 1745 (CO) cm^{-1}. Anal. Calcd for $C_{22}H_{41}O_6N$: C, 63.58; H, 9.95; N, 3.37. Found: C, 63.72; H, 10.05; N, 3.38.

1-[[*N*-[3-(tert-Butoxycarbonyl)-1,1-bis[2-tert-butoxycarbonyl)ethyl]propyl]amino] carbonyl]adamantane. A solution of 1-adamantanecarbonyl chloride (1 g, 5 mmol), amine monomer (2.1 g, 5 mmol), and Et_3N (600 mg, 6 mmol) in dry benzene (25 mL) was stirred at 25°C for 20 hours. The mixture was washed sequentially with aqueous $NaHCO_3$ (10%), water, cold aqueous HCl (10%), and brine. The organic layer was dried (Na_2SO_4) and then concentrated in vacuo to give a residue which was chromatographed (SiO_2), eluting first with CH_2Cl_2 to remove some by-products and then with EtOAc to give a 71% yield of the ester as a white solid: 2 g; mp 84-86°C; ^1H NMR δ 1.46 (s, CH_3, 27 H), 1.68-2.1 (m, C*H*, C*H*$_2$, 27 H), 4.98 (bs, NH, 1 H); ^{13}C NMR δ 28.0 (CH_3), 28.2 (γ-CH), 29.8, 30.1 ($NHCCH_2CH_2CO$), 36.4 (δ-CH_2), 39.2 (β-CH_2), 41.2 (α-C), 56.7 (NHC), 80.5 (CCH_3), 172.8 (COO), 177.4 (CONH); IR (KBr) 3350, 2934, 2846, 1740, 1638, 1255, 1038 cm^{-1}, Anal. Calcd for $C_{33}H_{55}O_7N$: C, 68.58; H, 9.60; N, 2.43. Found: C, 68.36; H, 9.66; N, 2.36.

1-[[*N*-[3-[[*N*-[3-(tert-Butoxycarbonyl)-1,1-bis[2-(tert-butoxycarbonyl)ethyl]propyl]-amino]carbonyl]-1,1-bis[2-[[*N*-[3-(tert-butoxycarbonyl)-1,1-bis[2-(tert-butoxycarbonyl)-ethyl]propyl]amino]carbonyl]ethyl]propyl]amino]carbonyl]adamantane. A mixture of the triacid 1-[[*N*-[3-carboxy-1,1-bis(2-carboxyethyl)propyl]-amino]carbonyl]adamantane (400 mg, 1 mmol) amine monomer (1.45 g, 3.5 mmol), DCC (620 mg, 3 mmol), and 1-hydroxybenzotriazole (400 mg, 3 mmol) in dry DMF (15 mL) was stirred at 25°C for 48 hours. After filtration of the dicyclohexylurea, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and sequentially washed with cold aqueous HCl (10%), water, aqueous $NaHCO_3$ (10%), and brine. The organic phase was dried (Na_2SO_4). Removal of solvent in vacuo gave a thick viscous residue, which was flash chromatographed (SiO_2) eluting first with EtOAc/CH_2Cl_2 (1:1) then with 5% MeOH in EtOAc, furnished A 61% yield of the ester, as a white solid: 970 mg; mp 115-118°C; ^1H NMR δ 1.42 (s, CH_3, 81 H), 1.64-2.20 (m, C*H*, CH_2, 63 H), 5.88 (bs, NH, 4 H) ^{13}C NMR δ 27.9 (CH_3), 28.4 (γ-CH), 29.6, 30.0 (NHC$CH_2$$CH_2$COO), 31.6, 32.2 (NHC$CH_2$$CH_2$CONH), 36.6 ($\gamma$-$CH_2$), 39.2 ($\beta$-$CH_2$), 41.1

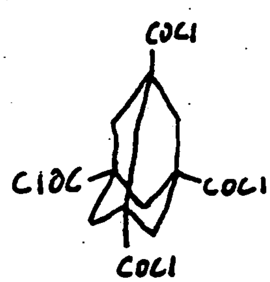
(α-C), 57.0 ($NHCCH_2CH_2COO$), 57.6 ($NHCCH_2CH_2CONH$), 80.3 (CCH_3), 172.6 (COO), 177.0 (CONH); IR (KBr) 3348, 2936, 2850, 1740, 1665, 1260, 1040 cm^{-1}. Anal. Calcd for $C_{87}H_{148}O_{22}N_4$: C, 65.22; H, 9.31; N, 3.50. Found: C, 65.41; H, 9.30; N, 3.39.

1-[[N-[3-[[N-[3-Carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl]-1,1-bis[2-[[N-[3-carboxy-1,1-bis(2-carboxyethyl)propyl]-amino]carbonyl]ethyl]propyl]amino]carbonyl]-adamantane. A solution of the above tert-butyl ester (800 mg, 500 μmol) in formic acid (96%, 5 mL) was stirred at 25°C for 12 hours. The solvent was removed in vacuo to give a residue; toluene (5 mL) was added and the solution was again evaporated in vacuo to azeotropically remove residual traces of formic acid. The resulting white solid was extracted with warm acetone (5x50 mL). The combined extract was filtered (SiO_2), eluting with acetone. The residue obtained after concentration was dissolved in aqueous NaOH (10%) and acidified with concentrated HCl to give a 95% yield of the acid as a white solid: 520 mg, mp 346°C dec; ^1H NMR (Me_2SO-d_6) δ 1.82-2.40 (m, CH, CH_2, 63 H), 4.45 (bs, OH, 9 H, exchanged with D_2O), 6.28 (bs, NH, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 29.6 (γ-CH), 30.2

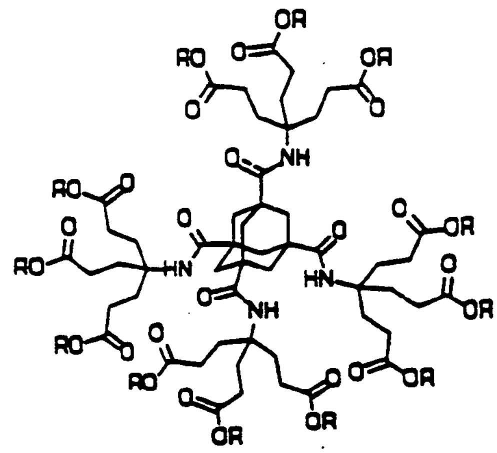
(NHCCH_2CH_2COOH), 31.0, 32.4 (NHCCH_2CH_2CONH), 37.8 (δ-CH_2), 40.1 (β-CH_2), 42.5 (α-C), 58.0 (NHCCH_2CH_2CONH), 58.4 (NHCCH_2CH_2COOH), 177.6 (COOH), 179.8 (CONH); IR (KBr) 3360, 3340-2600, 2900, 1744, 1690, 1245, 1090 cm^{-1}. Anal. Calcd for $C_{51}H_{76}O_{22}N_4$: C, 55.83; H, 6.98; N, 5.11. Found: C, 55.71; H, 7.04; N, 4.98.

The monomers of the present invention can be used for the design and synthesis of novel dendritic polymers which are one, two, three, or four-directional. In accordance with the present invention, the monomers can be used to synthesize four-directional spherical dendritic macromolecules based on adamantane. The use of the aminotrialkanoate monomer offers several advantages. The t-butyl ester intermediates are easily purified solids. Further, only two steps are required to progress from generation to generation.

A specific example of a synthesis is as follows. An acid chloride of the following formula



is treated with the aminotrialkanoatee present invention to afford a dodecaester of the following formula



HCO_2H (49 (R = t-Bu)
50 (R = H)

wherein R=t-Bu.

The dodecaester was hydrolyzed in good yield with 96% formic acid to yield the corresponding dodecaacid.

Addition of further tiers was easily obtained by the coupling of the dodecaacid and further layers of the aminotrialkanoate with DCC an 1-HBT to afford the ester wherein R=TBu. Upon hydrolysis, the ester quantitatively generated the corresponding next tiered polyacid.

A specific example of the method of forming the above-mentioned acid moiety is as follows.

1,3,5,7-Tetrakis{[*N*-[3-(<u>tert</u>-butoxycarbonyl)-1,1-bis[2-(<u>tert</u>-

butoxycarbonyl)ethyl]propyl]amino]carbonyl}-adamantane. A mixture of adamantanetetra-carboxylic acid (78 mg, 250 μmol) and freshly distilled $SOCl_2$ (2 mL) was refluxed for 4 hours. Excess of $SOCl_2$ was removed <u>in vacuo</u>, benzene (5 mL) was added, and the solution was concentrated <u>in vacuo</u> to yield the corresponding tetraacyl chloride, as a white solid.

Crude 1,3,5,7-Tetrakis(chlorocarbonyl) adamantane, amine monomer (450 mg, 1.1 mmol), and Et_3N (110 mg, 1.1 mmol) in dry benzene (10 mL) were stirred at 25°C for 20 hours. Additional benzene (40 mL) was added, and the mixture was sequentially washed with aqueous $NaHCO_3$ (10%), water, cold aqueous HCl (10%), and brine. The organic phase was dried (Na_2SO_4) and then concentrated <u>in vacuo</u> to furnish a viscous oil, which was chromatographed (SiO_2), eluting with 5% MeOH in EtOAc to generate a 61% yield of the dodecaester, as a white solid: 290 mg; mp 105-107°C; ^1H NMR δ 1.40 (s, CH_3, 108 H), 172 (s, CH_2, 12 H), 2.24 (m, CH_2, 48 H), 5.88 (bs, NH 4 H); ^{13}C NMR δ 28.1 (CH_3), 30.0, 30.4 (CCH_2CH_2COO), 39.0 (β-CH_2), 42.8 (α-C), 57.1 (HNC), 80.2 (CCH_3), 173.1 (COO), 177.6 (CONH); IR (KBr) 3348, 2930, 2845, 1740, 1645, 1260, 1038 cm^{-1}. Anal. Calcd

for $C_{102}H_{172}O_{28}N_4$: C, 64.38; H, 9.12; N, 2.95. Found: C, 64.52; H, 8.91; N, 2.86.

1,3,5,7-Tetrakis{[*N*-[3-carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl}-adamantane. A solution of the dodecaester (190 mg, 100 μmol) in formic acid (96%, 2 mL) was stirred at 25°C for 20 hours. Excess solvent was removed in vacuo, and toluene (3x2 mL) was added. The solvents were removed in vacuo to give a 94% yield of the dodecaacid, as a white solid: 115 mg; mp 282-284°C dec; ^{1}H NMR (D_2O) δ 1.84 (s, CH_2, 12H), 2.34 (m, CH_2, 48H); ^{13}C NMR (D_2O) δ 30.1 (CCH_2CH_2COOH), 38.8 (β-CH_2), 42.7 (α-C), 58.6 (HNC), 177.8 (COOH), 180.4 (CONH); (KBr) 3360, 3330-2600, 2903, 1745, 1690, 1245, 1090 cm^{-1}. Anal. Calcd for $C_{54}H_{76}O_{28}N_4$: C, 52.75; H, 6.23; N, 4.56. Found: C, 52.59; H, 6.22; N, 4.51.

1,3,5,7-Tetrakis{[*N*-[3-[[*N*-[3-(tert-butoxycarbonyl)-1,1-bis[2-(tert-butoxycarbonyl)-ethyl]propyl]amino]carbonyl]-1,1-bis[2-[[*N*-[3-(tert-butoxycarbonyl)-1,1-bis[2-(tert-butoxycarbonyl)ethyl]propyl]amino]carbonyl]-ethyl]propyl]amino]carbonyl}adamantane. A mixture of the dodecaacid (74 mg, 60 μmol), the amine monomer (330 mg, 790 μmol), dicyclohexyl-carbodiimide (DCC; 150 mg, 720 μmol), and 1-

hydroxybenzotriazole (100 mg, 740 μmol) in dry DMF (3 mL) was stirred at 25°C for 48 hours. After filtration of dicyclohexylurea, the solvent was removed _in vacuo_ to give a residue, which was dissolved in EtOAc (25 mL) and was sequentially washed with cold aqueous HCl (10%), water, aqueous $NaHCO_3$ (10%), and brine. The organic phase was dried (Na_2SO_4) and concentrated _in vacuo_, and the residue was chromatographed (SiO_2), eluting first with EtOAc/CH_2Cl_2 (1:1) to remove some impurities and then with 5% MeOH in EtOAc to furnish a 58% yield of the ester, as a white solid: 200 mg; mp 138°C; ^{1}H NMR δ 1.40 (s, CH_3); ^{13}C NMR δ 28.1 (CH_3), 30.0 (CCH_2CH_2CONH), 29.8, 30.2 (CCH_2CH_2COO), 38.9 (β-CH_2), 42.4 (α-C), 57.2 (*C*CH_2CH_2COO), 57.6 (*C*CH_2CH_2CONH), 80.0 (*C*CH_3), 172.8 (COO), 177.8 (CONH); IR (KBr) 3350, 2938, 2846, 1740, 1680, 1260, 1045 cm^{-1}. Anal. Calcd for $C_{318}H_{544}O_{88}N_{16}$: C, 63.64; H, 9.14; N, 3.74. Found: C, 63.28; H, 8.96; N, 3.77.

1,3,5,7-Tetrakis{[*N*-[3-[[*N*-[3-carboxy-1,1-bis(2-carboxyethyl)propyl]amino]carbonyl]-1,1-bis[2-[[*N*-[3-carboxy-1,1-bis(2-carboxyethyl)-propyl]amino]carbonyl]ethyl]propyl]amino]-carbonyl}adamantane. A solution of the ester (150 mg, 25 μmol) in formic acid (96%, 2 mL) was

stirred at 25°C for 20 hours. Workup and purification, similar to that of the dodecaacid, gave (95%) the corresponding acid, as a very hygroscopic solid: mp 350-354°C dec; ^1H NMR (D_2O) δ 1.80 (s, CH_2, 12 H), 2.18-2.41 (m, CH_2, 192 H); ^{13}C NMR (D_2O) δ 30.2 ($C\mathit{C}H_2\mathit{C}H_2COOH$), 30.8, 31.6 ($C\mathit{C}H_2\mathit{C}H_2CONH$), 39.1 ($\beta$-$CH_2$), 42.8 ($\alpha$-C), 58.1 ($\mathit{C}CH_2CH_2CONH$), 58.5 ($\mathit{C}CH_2CH_2COOH$), 178.0 (COOH), 180.2 (CONH); IR (KBr) 3360, 3340-2600, 2920, 1745, 1685, 1240, 1060 cm^{-1}.

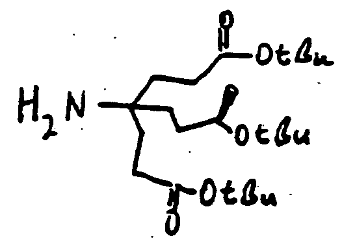
The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

Obviously many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims the invention may be practiced otherwise than as specifically described.

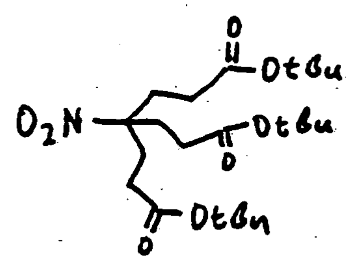
CLAIMS

What is Claimed is:

1. A method of forming an amine monomer of the formula



by the steps of reacting nitromethane and CH_2=$CHCO_2$-TBu by nucleophilic addition to form the triester nitrotrialkanoate of the formula

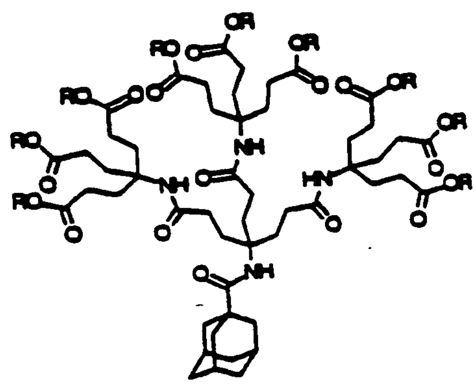


and reducing the nitrotrialkanoate to said amine monomer.

2. A method as set forth in claim 1 wherein said reacting step is further defined as reacting said methyl nitromethane and CH_2=$CHCO_2$-TBu in the presence of dimethoxyethane and Triton-B at a temperature of about 70° to 80°C for about one hour.

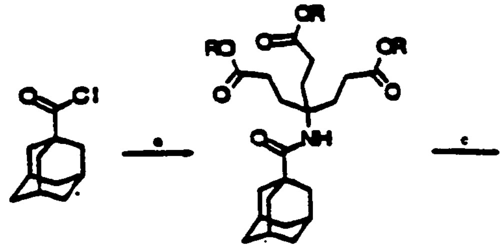
3. A method as set forth in claim 1 wherein said reducing step is further defined as reducing the nitrotrialkanoate to the amine monomer with T-1 Raney nickel at a temperature of about 60°C.

4. A method of forming a one-directional arborol of the formula



a 15 (R = *t*-Bu)
16 (R = H)

wherein R is t-Bu by the steps of treating adamantanecarbonyl chloride with di-<u>tert</u>-butyl 4-amino-[2-<u>tert</u>-butoxy-carbonyl)ethyl]-heptanedioate (amine monomer) to form a triester of the formula



a (R = *t*-Bu)
(R = H)

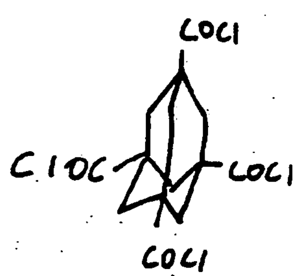
wherein R is TBu and hydrolyzing said triester to a triacid, and peptide coupling amine monomers to each of the acid moieties of said triacid to form said arborol.

5. A method as set forth in claim 4 wherein said treating step is conducted in the presence of NEt_3 and C_6H_6 at about 25°C for about 20 hours.

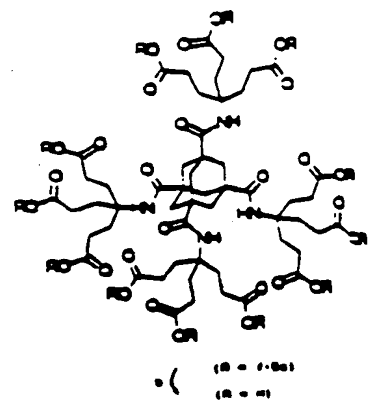
6. A method as set forth in claim 4 wherein said hydrolysis step is conducted in the presence of 96% HCO_2H at about 25°C for about 20 hours.

7. A method as set forth in claim 4 wherein said peptide coupling step is conducted in the presence of DCC, 1-hydroxybenzotriazole, and dimethylformamide at about 25°C for about 24 hours.

8. A method of forming a four-directional spherical dendritic macromolecule by the steps of treating an acid chloride of the formula

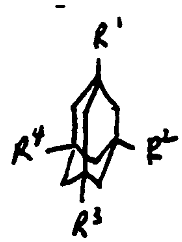


with an amine monomer, di-tert-butyl 4-amino-[2-(tert-butoxycarbonyl)ethyl]heptanedioate, to form a dodecaester of the formula



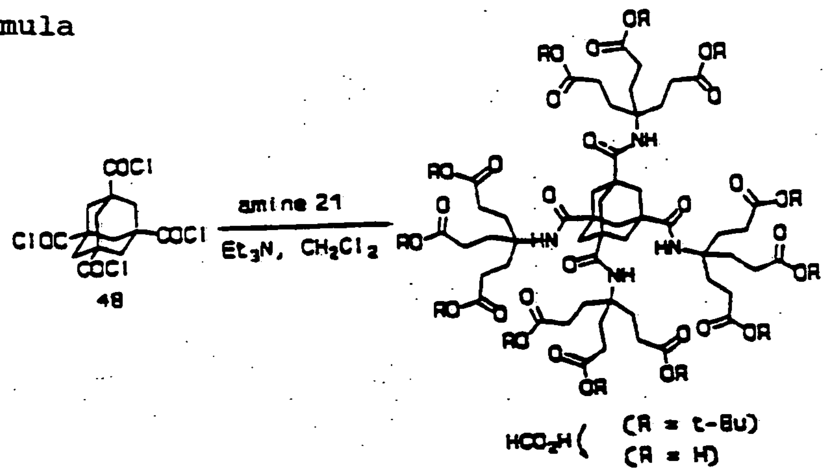
wherein R is t-Bu and adding additional layers of amine monomer by repeatedly hydrolyzing the ester, coupling the amine monomer to the acid moieties to form an additional tier of ester moieties and hydrolyzing to a corresponding acid.

9. A compound of the formula

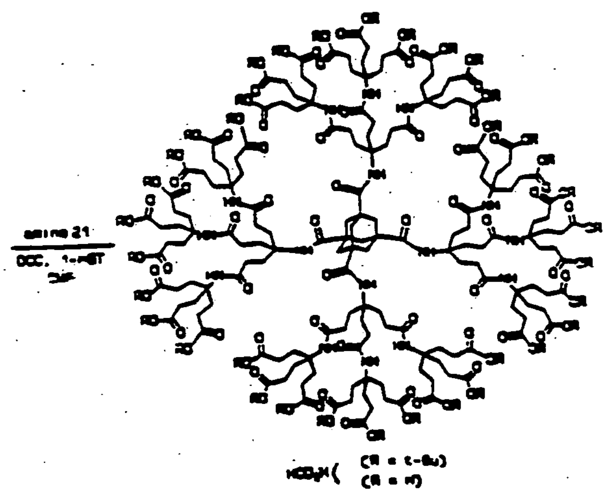


wherein R^1,R^2,R^3 and R^4 are selected from the group consisting of hydrogen and cascade arborol branches, at least one of said R^1,R^2,R^3 and R^4 being a cascade arborol branch.

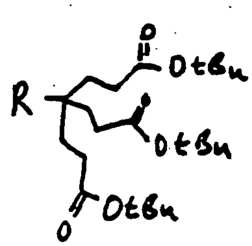
10. A compound of claim 9 of the formula



11. A compound as set forth in claim 9 of the formula

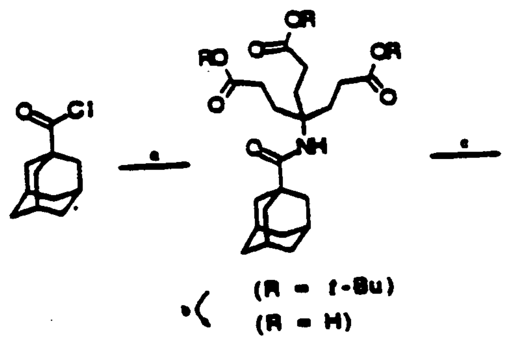


12. A compound of the formula

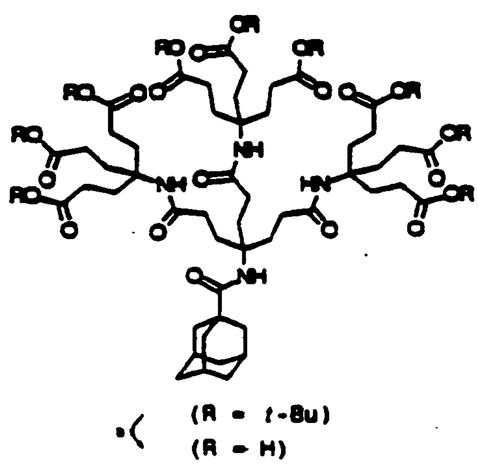


wherein R is selected from the group consisting essentially of NH_2 and NO_2.

13. A compound of the formula



14. A compound of the formula



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/03616

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 61/12, 69/74, 205/00, 229/00
US CL :560/117, 156, 171; 562/499
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 560/117, 156, 171; 562/499

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US, A, 2,342,119 (Bruson) 22 February 1944 See Example 6	12 1-3
X A	US, A, 2,502,548 (Allen, et al.) 04 April 1950 See Example VI.	12 1-3
X	US, A, 3,642,843 (Nemec, et al.) 15 February 1972 See Example 10.	13
A	US, A, 4,454,327 (Butler) 12 June 1984 See Example A.	1-3
X A	Journal of Organic Chemistry, Vol. 55, issued 1990, C.D. Weis, 'Facile Elimination of Nitrous Acid from Quaternary Nitroalkanes', see pages 5801 to 5802.	12 1-3

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 JULY 1993	AUG 30 1993

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MICHAEL L. SHIPPEN for
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/03616

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Organic Chemistry, Vol. 56, issued 1991 December, G.R. Newkome, 'Cascade Polymers', See pages 7162-7167.	1-14
O, X	Journal of Organic Chemistry, Vol. 57, issud 1992 January, G.R. Newkome, 'Cascade Polymers', See pages 358 to 362.	1-14
X	Aldrichimica Acta; Vol. 25, no. 2, issued 1992, G.R. Newkome, 'Building Blocks for Dendritic Macromolecules', See pages 31 to 38.	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/03616

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(Form PCT/ISA/206 Previously Mailed.)

Group I. Claims 1-3 and 12, drawn process of forming an amine monomer and the product, classified in Class 560, subclasses 155 and 171.

Group II. Claims 4-11, 13 and 14, drawn to process of preparing arborol compounds and the product, classified in Class 560, subclass 169.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.